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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,156	12/05/2003	Shaomeng Wang	UM-08477	1029

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,156	WANG ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,27-41,43-47,49,50 and 52-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,27-41,43-47,49,50 and 52-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-23-06,10-17-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed April 7, 2006 have been entered.

Claims 52-96 have been added. Claims 3-26, 42, 48, and 51 have been cancelled.

Claims 1, 2, 27-41, 43-47, 49, 50, 52-96 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2, 27-41, 43-47, 49-50, 52-53, 63-65, 69-93, and 95-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gossypol compounds that are having aldehyde groups and isopropyl group, does not reasonably provide enablement for apogossypol, the Schiff's base thereof that do not have aldehyde group on the gossypol compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide sufficient information to one of skilled in the art to practice the instant invention.

The claims are directed to a method of treating proliferative disease, such as cancer. In the instant specification, only (-)-gossypol is demonstrated to have anti-tumor activity. Shelley, et al., Anticancer Drugs, 2000;11(3):209-216, clearly teaches that **apogossypol** and the **Schiff's base of gossypol** are inactive against four tumor cell lines (See page 212, Figure 2). Shelley et al. further discusses that the reasons for apogossypol and the Schiff's base of gossypol to be inactive is due to the fact that the aldehyde groups are missing (See page 214, col. 2).

Furthermore, the **ethyl derivatives of gossypol** show negligible inhibitory activity to the tumor cell lines similar to that of the Schiff's base derivatives (See page 214, col. 2, second paragraph). In other words, the evidence is clear that "when both of the aldehydes are blocked, forming the individual *l*- and *d*-bis Schiff's bases, the cytotoxicity activity is abolished." See page 214, last sentence bridging to page 215, first paragraph). Since the instant specification only demonstrates the activity of (-)-gossypol, there is no information as to how other derivatives, which without the aldehyde groups nor the isopropyl group, might be useful in a method of treating proliferative disorders. The instant specification fails to provide sufficient information to one skilled in the art to practice the full scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-62 and 78-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,114,397 ('397) from IDS filed October 17, 2005 in view of Merck Manual of Diagnosis and Therapy, 16th ed., 1992, pages 1275-1277.

'397 teaches a method and composition of employing gossypol, gossypol acetic acid, gossypolone and metabolites as effective in treating cancer (See for example the abstract and claims 1-14). '397 also teaches gossypol can be combined with other anti-cancer therapeutic agents such as cisplatin in a method and composition of treating cancer (see abstract and col. 2, line 65 - col. 3, line 11).

'397 does not expressly teach the use of radiation in combination with gossypol compounds to treat cancer. '397 does not expressly teach the herein recited regimen of the compounds used such as route of administrations and the sequence of administration. '397 does not expressly teach the method of treating cancer employs the optical isomers gossypol compounds.

Merck Manual teaches that radiation is one of the common modalities in cancer treatment (See page 1276-1277).

It would have been obvious to one of ordinary skill in the art at the time of invention to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. It would have been obvious to one of ordinary skill in the art at the time of invention to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation.

One of ordinary skill in the art would have been motivated to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. Since both radiation and gossypol compounds of '397 are known to be useful in treating cancer individually, combining them in a composition or concomitantly employing them in a method of treating the very same disease (i.e., cancer) would be prima facie obvious, at least additive effect would be expected. '397 teaches a chiral center in the claimed compound, and illustrated separation for such optical isomers. It is well settled patent law that the skilled artisan, knowing a compound contains an asymmetric carbon atom, possesses all resultant optical isomers. The skilled artisan in possession of the designated compounds, possesses all isomeric forms of the compound for the old and well known antitumor utility. It is well known in the pharmaceutical art that various optical isomers will exhibit biological effects at various levels. Absent some difference in kind between the various isomers the skilled artisan would have seen each isomer as *prima facie* obvious (see *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960)). The skilled artisan would have expected optical isomers to be separable and isomers so separated to exhibit physiological effects at varying levels. Possessing a compound known to contain chiral centers, places all the resultant compounds in the skilled artisan's possession. It

would follow therefore, the instant claims recite *prima facie* obvious subject matter and are properly rejected under 35 USC 103.

One of ordinary skill in the art would have been motivated to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation since optimization of the resulted parameters (e.g., dosage and regimen) is routinely done in the art and thus obvious as being within the purview of skilled artisan.

Examiner notes that the herein claimed mechanism of action of gossypol must be present in the method suggested by the cited prior arts since the products and its intrinsic properties cannot be separated.

Claims 1,2 27-41, 43-47, and 49-50, 52-62, 66-68, 78-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shelley et al., in view of '397 and Merck Manual.

Shelley et al. teaches gossypol, gossypolone, and its derivatives, which have isopropyl moeity and aldehyde moiety, exhibiting anti-tumor activity (See the discussion above).

Shelley et al. does not expressly teach hemigossypolone in a method of treating tumor. Shelley et al. does not expressly teach the secondary chemotherapeutic agent or radiation therapy. Shelley et al. does not expressly teach the herein claimed dosage or dosing regimen to treat tumor.

'397 teaches '397 teaches a method and composition of employing gossypol, gossypol acetic acid, gossypolone and metabolites as effective in treating cancer (See for example the abstract and claims 1-14). '397 also teaches gossypol can be combined with other anti-cancer

therapeutic agents such as cisplatin in a method and composition of treating cancer (see abstract and col. 2, line 65 - col. 3, line 11).

Merck Manual teaches that radiation is one of the common modalities in cancer treatment (See page 1276-1277).

It would have been obvious to one of ordinary skill in the art at the time of invention to employ gossypolone derivative hemigossypolone in a method of treating tumor. It would have been obvious to one of ordinary skill in the art at the time of invention to incorporate a secondary agent into the method and composition of treating tumor. It would have been obvious to one of ordinary skill in the art at the time of invention to employ the herein claimed dosage and dosing regimen in a method of treating tumor.

One of ordinary skill in the art would have been motivated to employ gossypolone derivative hemigossypolone in a method of treating tumor. It is clear from Shelley's experiment that the antitumor activity is responsible by the aldehyde group and the isopropyl group in the gossypol or gossypolone molecules. Therefore, as long as it maintain the two active groups, responsible for the anti-tumor activity, gossypol derivatives, such as hemigossypolone, would be reasonably expected to have the similar anti-tumor activity. Therefore, employing hemigossypolone in a method of treating tumor would be reasonably expected to be effective. One of ordinary skill in the art would have been motivated to incorporate a secondary agent into the method and composition of treating tumor. Since both radiation and/or cisplatin and gossypol or derivatives such as hemigossypolone are useful in treating cancer individually, combining them in a composition or concomitantly employing them in a method of treating the very same disease (i.e., cancer) would be prima facie obvious, at least additive effect would be expected.

Furthermore, one of ordinary skill in the art would have been motivated to employ the herein claimed dosage and dosing regimen in a method of treating tumor since optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan. As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, including by orders of magnitude; for instance, an extremely heavy patient or one having an unusually severe infection would require a correspondingly higher dosage. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. For these and other self-evident reasons, it would have been obvious to have adjusted the dosages to the herein claimed dosage and regimen.

Response to Arguments

Applicant's arguments filed April 7, 2006 averring the presence of unexpected synergistic effect have been fully considered but they are not persuasive. Examiner notes that unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the unexpected results are not commensurate with the scope of the subject matter claimed. In the instant specification, only (-)- gossypol with certain chemotherapeutic agents are tested and shown unexpected benefits against only a few

types of tumor cell lines. The claims are much broader than the unexpected synergistic results shown. Therefore, the prior arts still render the instant claims obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617